Pathogenesis and Rx of Covid

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Introduction

This article serves to inform the understanding of the pathogenesis of Covid 19, and in so doing, help guide protocols for outpatient treatment and management of the pandemic.

Currently there are no outpatient treatment recommendations, and there is a distinct lack of understanding of the disease progression. This is most likely due to the absence of outpatient examination, treatment and follow up of patients because of isolation measures and current protocols. There is however a wealth of information around hospital presentations, investigations and pathological findings. Hospital treatment protocols are based on these findings, but have thus far not been universally consistent in efficacy and outcome. This has thus created controversy and confusion as to the pathogenesis and treatment of Covid 19.

Over the past 5 months, my staff and I have examined, treated and followed up on over 200 symptomatic Covid patients, some critically ill. In doing so, I used the information gathered to refine my understanding of the pathogenesis of Covid and thus adjust treatment protocols.

This has resulted in some remarkable yet consistent and predictable results and recoveries. In all, we have had no deaths, no hospitalizations and complete recoveries of all patients, even those with severe dyspnea. Most confirmatory to my theory of the pathogenesis were the 12 most dyspneic patients with low 80% SpO2 that recovered to over 96% SpO2 within 24 to 36 hours of treatment, without the need for hospitalization or oxygen. All dyspneic patients had normal SpO2 within 3 days of treatment.

The information thus gathered can prevent most of the mortality and morbidity from Covid 19. The furthering of understanding of the pathogenesis of Covid 19 can guide future research and intervention strategies to negate the effects of the pandemic.

Virus, Detection and Symptoms

RNA Virus. Airborne transmission. Common in stool samples..? Waterborne transmission. Highly contagious but infectivity and virulence unknown due to lack of understanding of pathogenesis of Covid, and testing limitations. Enters cell through ACE 2 receptors.

Like other common RNA viruses, uses cell machinery to replicate and burst out copies, leaving behind dead cell debris and inflammation, that could result in mild scarring Average duration of symptoms 3 to 6 days with host non infective after day 7.

Laboratory Detection. Swabs vary greatly in isolating the virus. Technique, compounded by untrained screeners, Area swabbed etc.

PCR test very specific but not very sensitive, about 65%, so about 35% False negatives, and so, cannot be used for diagnosis or confirmation of diagnosis. Only useful for screening purposes but not sensitive enough to guide detection and isolation/quarantine measures. Absolute numerical data is not a true reflection, ratios may yield better insight. ? Antibody testing for more reliable data.

Clinical Presentation as directly observed.

Infects URT. Sore throat, loss of smell, loss of sweet and salty taste, bitter preserved. Generalised body ache, fever with chills.

Spreads lower. Dry persistent cough, cold feeling between shoulder blades, burning sensation in chest, tightness with scanty clear sputum.

Bacterial Co-infection. Productive cough with purulent sputum, sinusitis with purulent mucus, earache etc. The above symptoms are progressive over the first 6 days of infection and may lead to a pneumonia with associated dyspnea.

A significant proportion of infected symptomatic individuals develop dyspnea from day 7 onwards, irrespective of severity or duration of initial symptoms. Common associated symptoms are mild generalized body pain and fatigue to the point of having to sleep. This dyspnea can be of sudden onset and rapidly progressive, leading to severe hypoxemia and SpO2 drop to below 85%

in 2 days. It is more commonly insidious in onset and persistent for a variable duration, with SpO2 in the mid to low 90s, and may result in diffuse lung fibrosis the longer it persists. It is during this period that the rashes, neurologic symptoms and end organ damage are also reported.

GIT infection common. Usually preceded by a sore throat that spontaneously resolves in a day or two, heartburn, nausea, short severe intermittent abdominal cramps with tinkles and gurgling, severe diarrhea that slows to a poorly formed, sometimes slimy stool in 4 to 5 days.

Other reported symptoms. Conjunctivitis, variety of skin rashes, distal ischemic digit injuries, varied neurologic symptoms, symptoms of organ injury or failure.

Case Morphology

Understanding the progression of this illness also requires an overview of the facts as they currently are, as compared to the facts as we know them to be.

We Know

Viruses are generally quite specific in the type of tissue they infect. Their infections are generally self-limiting, opportunistic, and seldom cause death. Mortality is usually due to some other predisposition, either natural or chronic illness related.

Respiratory viruses cause symptoms ranging from none (most), to a mild sore throat which passes in a few days, or spreads lower, and can complicate with a bacterial infection ranging from mild bronchitis to pneumonia, with typical radiologic findings. These symptoms are progressive and well understood, and these typical case presentations should be removed from analysis, to help concentrate on what we don't know.

Facts as they are:

What we have left are case histories that don't fit the profile above, are atypical for a single virus, and don't show typical disease progression and rates.

Unusual symptoms:

Hypoxemia poorly correlated to levels of dyspnea. Sudden, rapidly progressive dyspnea and SpO2 drop, in an otherwise healthy patient, resulting in poor outcomes.

Slow chronic hypoxemia with variable chronic lung damage from fibrosis over variable duration. Associated with a persistent, dry cough with or without wheezing.

Mild SpO2 drop, not below 92% and may need intermittent oxygen. Usually resolves spontaneously in a few days to a week.

Autopsy findings: Lungs are edematous and heavy with microvascular clots. Multiple organ involvement usually due to hypoxic injury, DIC. Or immune/inflammatory response, rather than direct viral infection.

Chronic manifestations: COPD, Kawasaki like illness in children, Hypoxic injuries, Thromboembolic injuries, Diabetes.

Unusual outcomes:

If we remove the usual risk factor related outcomes, that would complicate any usual viral infection, what we are left with is poor age and health status correlation. Fit, healthy 25 year olds have succumbed suddenly, and high risk 90 year olds got through uneventfully. Patients with mild prolonged illness present back in a few months with chronic disease, commonly COPD, and Diabetes.

Men are more at risk, multiple intra family fatalities related to risk of infection, and or genetic predisposition? Many father and son deaths with mother spared, and vice versa, but less commonly.

Varying mortality rates between countries and ethnicities. Children below 10 years old are least at risk.

Pathogenesis from Morphology

It is clear from the case morphology that a viral infection alone cannot explain the diversity of symptoms, unusual presentations and unusual outcomes.

At this juncture, it is again important to take an overview, being considerate of the wealth of information available around the pathogenesis of a variety of conditions, to find the best fit for the unusual presentations and outcomes we see.

The only pathogenesis that fully explains these outcomes are Type 1 Hypersensitivity reactions, the allergic reactions we have to external allergens, whether inhaled, ingested, or contacted. These reactions consist of an Initial acute phase that lasts a few hours to a few days, and can be mild to fatal. They sometimes progress to a Late phase reaction that lasts for a week or so, but results in cell damage and other immune implications. Reactions to the same allergen vary in speed, severity, duration and symptoms, and if not treated, would have diverse outcomes, ranging from sudden anaphylactic type reactions leading to rapid deterioration and death, to moderate chronic allergic reactions resulting in scarring and collateral immune mediated injuries, to mild transient localized reactions.

In my opinion, and from my examination, treatment and review of over 200 Covid patients, the initial Corona virus infection is like any other common respiratory virus infection, with a spread of statistics in similar ratios to previous epidemics, during the initial 7 days.

On around the 7th day, a Type 1 Hypersensitivity reaction is triggered in the lungs, probably to a recognizable viral protein fragment, leading to the variety of presentations and outcomes we see, including chronicity and complications due to non-treatment. This reaction would not be directly related to age, comorbidities etc., but directly related to genetic predisposition and immune maturity, or lack thereof.

It explains the sudden deterioration in lung oxygen exchange capacity and SpO2, in asymptomatic, and mild transient viral illness, at around the 7th day. The speed of deterioration varies greatly, and can complicate an otherwise uneventful recovery of a high risk patient post day 7.

Those that have severe initial Type 1 reactions, present with sudden onset dyspnea with steadily declining SpO2, can deteriorate rapidly, and are at high risk of mortality. However, some with milder initial reactions progress to late stage Type 1 Hypersensitivity reactions, present with persistent dry cough, symptoms of mild hypoxia or hypoxic injury etc., with mild but prolonged SpO2 drop, and these will have varying degrees of lung damage over time.

Many of the reported chronic manifestations of Covid are explained by immune injury to the lungs, and collateral immune or hypoxic injury to other organs or systems.

The gastrointestinal symptoms are likely due to an initial viral gastroenteritis, followed by a prolonged allergic bowel inflammation and irritability, with chronic sequelae.

BCG vaccination and active PTB seem to modulate immunity and avert severe Type 1 reactions.

Patients on immunomodulatory treatments are less likely to have a severe Type 1 reaction.

Children's underdeveloped immunity is less likely to trigger a Type 1 reaction.

Generally, younger patients will have no reactions due to it being their first exposure to the allergen, and a reaction requires previous exposure. They will however, become sensitized, and subsequent exposure can provoke a more vigorous immune response. Those with mild to moderate initial reactions will become more TOLERANT to subsequent exposures. They will however, consequently become passive future transmitters of the virus.

Seeing that reports of reinfections are surfacing, could Type 1 reactions explain the prolonged second wave of infections that had higher mortality in the younger population (Sensitized individuals), and the shorter third wave with generally low mortality (Tolerance) during the Spanish Flu?

Treatment Toolbox

As I consider this disease to have two overlapping etiologies i.e. viral and allergic, treatment would differ depending on the point at which it is initiated.

OPD DRUGS BEING TRIED SO FAR.

Hydroxychloroquine has been very controversial and has historic prophylactic use against viral infection, and has shown some prophylactic benefit in trials on healthcare workers. It has anti-inflammatory, antihistaminic, smooth muscle relaxant and antiarrhythmic properties. This could have symptomatic benefit during the viral phase of Covid illness. Its immunomodulatory effect would be of more benefit in the allergic reaction, but may be too slow in onset to be of benefit, if started well into the initial 7 days. The immunomodulatory effect of Ivermectin may have a more rapid onset.

.Azithromycin has shown benefits in treating the usual and atypical bronchopneumonia complicating viral infections, and should be the antibiotic of choice in cases complicated by bacterial URTIs.

.Doxycycline has a wide range of effects, and through its inhibitory effects on protein synthesis, can potentially slow viral replication. This can potentially decrease symptom severity and infectivity of infected individuals.

.The viral phase of the illness is generally mild and self-limiting and symptomatic treatment would be sufficient in most.

DRUGS TO TREAT TYPE 1 HYPERSENSITIVITY REACTIONS

.Adrenaline is used to treat hypovolemic shock. Can also be used to nebulize patients with rapidly progressive reactions and severe dyspnea.

.Prednisone is indicated to suppress any sudden onset severe allergic reaction. Its use from day 7 onwards can be lifesaving. Use in the first 7 days can be detrimental and needs to be limited to life threatening illness in that period.

.Promethazine is the antihistamine of choice in Type 1 Hypersensitivity reactions. It can suppress all the immediate manifestations of Type 1 reactions rapidly and effectively. H2 antagonists may need to be added in those with gastrointestinal symptoms.

Montelukast is a leukotriene receptor antagonist, blocking the effects of cysteinyl leukotrienes, a unique feature not achieved by corticosteroids. It has both bronchodilator and anti-inflammatory activity. It is indicated in the prophylaxis and treatment of atopic conditions, and has benefit in preventing Type 1 reactions.

Beclometasone is an inhaled steroid that can suppress lung inflammation topically. It would be beneficial in patients with prolonged reactions with associated dry cough. It could also limit lung fibrosis and progression to COPD.

Other less common drugs that should have benefit are: Ipratropium bromide / Sodium Chromoglycate/ Ketotifen.

Protocol

VIRAL PHASE

Mild symptoms: Sore throat, loss of smell etc.

- Hydroxychloroquine 200mg dly x 5 days

- Montelukast 10mg dly x 1 month

- Symptomatic treatment

Moderate symptoms, present later into illness so enquire about day of onset of symptoms: Dry Cough, Mucopurulent bronchitis etc.

- Hydroxychloroquine 200mg dly x 5 days

- Azithromycin 500mg on day 1, then 250mg dly for 4 more days, or other more appropriate antibiotic

- Montelukast 10mg dly x 1 month

-Symptomatic treatment

Most patients recover quickly from mild symptoms. Those with moderate symptoms take a little longer.

All patients should be educated to be aware of new symptoms from day 7 onwards, even if completely well, and report immediately for treatment.

** These symptoms are usually: Generalised body aches and pains, fatigue, dyspnea, and decreasing SpO2. These herald the start of the Hypersensitivity reaction.

HYPERSENSITIVITY PHASE

Range of Presentation: Rapidly progressive dyspnea with SpO2 low 80% with or without chest symptoms to Slow prolonged SpO2 decrease, Prolonged cough, wheeze etc.

- Prednisone 50mg stat and decrease single dly morning dose by 5mg over next 9 days...50, 45, 40, 35mg mane..... Those who present with mild prolonged symptoms may need lower doses tapered over a longer period.

- Promethazine 25mg stat then tds x 5 days

- Adrenaline nebs stat if severe dyspnea or if hypotension suspected

- Aspirin prophylaxis mane x 1 month

- Montelukast 10mg nocte x 1 month

- Naproxen 250mg bd for fever, as it is from allergic inflammation, not infection. Paracetamol not effective alone.

- Beclate 200mcg inhaler bd for those with chronic dry cough (Topical steroid)

- ? Sodium Chromoglycate/ Ketotifen/Ipratropium bromide inhaler may give better results and possible prophylactic benefit

MANAGEMENT OF FUTURE INFECTIONS

Patients who do not develop a Hypersensitivity reaction during the initial infection are either previously unexposed, or tolerant. Specific IgE screening would identify those at risk of subsequent reactions, and significantly elevated levels of IgE would identify those prone to severe reactions. Montelukast would prevent these reactions and should be used prophylactically in those with elevated IgE levels.

Observations using Protocol

The following are observations made by my personal examination of over 200 Covid patients, using the above protocol to treat, and by monitoring Presentation and Progress till full recovery. Many observations confirm the existence of a Type 1 Hypersensitivity reaction.

Hydroxychloroquine started early helps symptomatically and can suppress the Hypersensitivity reaction on day seven. It is however less effective than other drugs in modulating immune hypersensitivity when started later on in the illness.

Doxycycline is being used prophylactically in a large group of (160) very highly exposed individuals (Teachers and Police on duty) over the past 3 months. Fewer in the group have so far become infected compared to their colleagues. The 4 that did become infected so far, had no to mild transient symptoms that resolved spontaneously during the viral phase. They were home isolated and did not have any of their close contacts test positive or exhibit symptoms over the duration of their illness. This may be indication of Doxycycline's suppressive effect on viral

replication and consequently on viral transmission. However, 3 went on to develop dyspnea on day 7, that resolved rapidly with treatment. Evaluation is ongoing.

All the other drugs used where dictated by bacterial infections and presenting symptoms, with their benefits reasonably obvious.

Patients presenting with dyspnea or decreased SpO2 after day 7 where immediately started on treatment as outlined. All had improvement in symptoms and SpO2 within 24 hours. The most telling was a group of the 12 most hypoxic patients, who all presented after day 7, with SpO2 in the low 80%. , all having severe dyspnea etc. Every one of them had symptomatic relief within a few hours and returned to >96% SpO2 within 24 to 36 hours of starting treatment. This was achieved with outpatient treatment, on Room Air without the need for oxygen, and all 12 made full recoveries in a few days.

All patients started on Montelukast in the first 7 days had no reaction on day 7 or thereafter. (About 80 symptomatic patients)

Prednisone, Promethazine and Montelukast proved to be lifesaving, and after seeing over 200 Covid patients and counting, we have not had a death, nor hospitalization of a patient. All recovered completely within 14 days of the onset.

No other medication in current use for the treatment of Covid 19 i.e. Remdesivir, Tocilizumab, Convalescent plasma, etc., have shown such rapid response and predictable outcome in severely ill patients, negating the need for oxygen and hospitalization.

Implications of Observations

The rapid response to the medications used to treat a Type 1 Hypersensitivity reactions confirm the existence of the same. This could have some serious implications for the future management of the Covid pandemic.

Monitoring for a Hypersensitivity reaction and prompt treatment would decrease morbidity and mortality significantly.

Those with mild to moderate initial illness will develop tolerance with subsequent exposure. However, those that were initially asymptomatic due to it being their first exposure, will become sensitized, and run the risk of subsequent reactions.

Identifying the specific IgE involved in this reaction and quantifying its levels would help identify those at risk. This would also help predict the severity of reaction to future exposure, and guide prophylactic and preventive treatment.

Vaccines against the virus would only benefit those that are Hypersensitive, and blanket vaccinations would be unnecessary and unsafe in view of the rush to bring it to market without long term evaluation. Being able to identify Hypersensitive individuals and provide appropriate information and treatment may negate the need for a vaccine altogether.

Conclusion

With the high mortality and morbidity from Covid 19, it is my wish that the information presented above will help save lives and guide further research and management. The protocol and its deficiencies provide a valuable starting point for further evaluation of treatment interventions.

I hope that I've brought some clarity during this difficult time.

Thanking you.

Dr Shankara Chetty.